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Resistance to apoptosis is a hallmark of cancer. Therefore, an important strategy to counteract this process is the search for anticancer drugs that cause apoptosis. Possible therapeutic targets are two of the important proteases responsible for the execution phase of apoptosis, the caspases-3 and -7.

In this work we used a yeast target-based screening to search for activators of caspases-3 and -7 from a library of several new prenylated flavonoids, followed by confirmation of the effect of the selected compounds in the human tumor cell lines HL-60 (acute promyelocytic leukemia) and MCF-7 (breast adenocarcinoma).

The yeast phenotypic assays showed two potential activators of caspase-7: the 5,6-dihydroxy-7-prenyloxyflavone and the 3-hydroxy-7-geranyloxyflavone. These two flavonoids did not interfere with caspase-3 activity in yeast, unlike the procaspase activating compound-1 (PAC-1), a standard activator of both caspases-3 and -7. Furthermore, activation of caspase-7 (from procaspase-7) was observed in both yeast and in vitro processing assays. In HL-60 and MCF-7 human tumor cells, the two flavonoids inhibited cell growth with higher potencies than PAC-1. This was particularly evident in MCF-7 cells, which lack caspase-3. In addition, in MCF-7 cells the two studied compounds were found to process procaspase-7, to increase its activity and to sensitize tumor cells for the effect of a cytotoxic drug (etoposide).

In summary, in this work simplified and efficient yeast target-based assays were established for the screening of modulators of caspases-3 and -7. With this yeast approach, potential small-molecule activators of caspase-7 with a flavonoid scaffold were identified for the first time. Their activity was supported by in vitro processing assays and by studies in human tumor cell lines. Finally, these two flavonoids may pave the way for the structure-based design of new classes of caspase activators with anticancer properties.

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